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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/532,374
Filing Date: April 21, 2005
Appellant(s): BERZOFSKY ET AL.

Anne Carlson
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 4/23/10 appealing from the Office action mailed 8/21/09.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 46-72 are pending, rejected and appealed.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the

subheading “WITHDRAWN REJECTIONS.” New grounds of rejection (if any) are provided under the subheading “NEW GROUNDS OF REJECTION.”

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant’s brief.

(8) Evidence Relied Upon

6,090,383	DASCH et al	7-2000
WO 00/01410	SUKHATME	1-2000
6,224,866	BARBERA-GUILLEM	5-2001
2005/0214307	ROSENBLUM	9-2005
6,297,041	ZAVADA et al	10-2001
2004/0197333	SUTHANTHIRAN et al	10-2004

Terabe, M. "NKT cell-mediated repression of tumor immunosurveillance by IL-13 and the IL-4R-STAT6 pathway" Nature Immunology, vol. 1, no. 6 (December 2000), pp. 515-520.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 46-50, 52-55, 59-67, 69 and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dasch et al US 6090383 in view of WO 00/01410, Barbera-Guillem US 6224866, Rosenblum US 2005/0214307 (filed 3/17/95) and Zavada et al US 6297041.

Dasch et al discloses and claims methods for treating tumor cells by administering monoclonal antibodies reactive to TGF-beta to suppress the immunosuppressive effects of TGF-beta and to permit generation of an immune response against the tumor and this results in tumor regression (col. 2, lines 28-32 and col. 5, lines 54-58). Tumors include sarcomas, melanomas and carcinomas (col. 2, lines 8-10 and col. 5, lines 48-50). The preferred monoclonal antibody is Mab 1D11.16 (which is the same one used by applicant, col. 5, lines 18+). The antibody neutralizes the biological activity of TGF-beta and prevents binding of antigen to cell surface receptors (col. 5, lines 58-60). The biological activities of TGF-beta include suppressing the proliferation of T and B cells and NK cells and that the Mab of the invention blocks the TGF-B's immunosuppressive effects. (col. 1, lines 20-40 and col. 5, lines 48+). The antibodies can be administered by intravenous injection or peritoneal perfusion or by bolus injection into the muscle or subcutaneous tissue (col. 6, lines 26-30) to patients (col. 6, lines 5-9).

This reference does not specifically discuss the treatment of tumor recurrence.

It is known in the art that compounds that treat tumors can also be used to treat tumor recurrence. WO 00/01410 discloses that antibodies against TGF-beta can be used in the treatment and diagnosis of proliferating cells and that these antibodies can also be used to detect tumor recurrences (see pages 23-24). Barbera-Guillem discloses that one skilled in art would readily recognize that the same procedure used for treating a cancer would also be used for the treatment of recurrence of the same cancer (col. 23, lines 20-25). It is also that the reference discloses antibody

therapy, which is the same type of therapy used by applicant. Rosenblum discloses that the same antibody used in treatment of tumors is used in the treatment of tumor recurrence (paragraph [0043]). Zavada et al discloses the same compounds (which include polypeptides and antibodies) can be used for treatment and treatment of recurrence (col. 10, line 50 to col. 11, line 10). Thus, the use of the same antibody in treatment of tumors is also used in the treatment of recurrent tumors.

Because it is well known in the art to use the same antibody used in treatment of a tumor as in the treatment of tumor recurrence, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to use the antibody of the primary reference in the treatment of tumor recurrence. This is even further supported by WO 00/01410 which discloses antibodies to TGF-beta to be used to in the diagnosis and treatment of proliferating cells and that the diagnosis also includes diagnosing tumor recurrence. In view of this one of ordinary skill in the art would immediately envisage that the same antibody that can detect tumor recurrence can also be used in the treatment of tumor recurrence. Furthermore, since both applicant and the primary reference use the exact same antibody and since the antibody has been shown in the primary reference to block the TGF-B's immunosuppressive effects (which include suppressing the proliferation of T and B cells and NK cells) and result in tumor destruction, the property of increased tumor immunosurveillance is an expected property of the antibody in the reference.

Claims 46-55, 59-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dasch et al US 6090383 in view of WO 00/01410, Barbera-Guillem US 6224866, Rosenblum US 2005/0214307 (filed 3/17/95) and Zavada et al US 6297041 and Suthanthiran et al US 2004-0197333 (filed 2/10/00).

Dasch et al, WO 00/01410, Barbera-Guillem, Rosenblum and Zavada et al have been discussed above.

The only difference between the instant invention and the combination of the references is the specific mention of the difference types of cancers and the humanized antibodies.

Suthanthiran et al discloses the use of TGF-beta antagonists, which includes monoclonal antibodies (abstract, [0024]) to treat a variety of different cancers known to be associated with TGF-beta. These include cancers of the breast, lung, small intestine (reads on gastrointestinal), colon, kidney, ovary, prostate, brain, pancreas, skin, bone, uterus, testicles, cervix and liver ([0019). This reference also discloses monoclonal antibodies and humanized antibodies to TGF-beta ([0028]-[0029]).

Therefore, in view of the fact that is it known that TGF-beta antagonists, including monoclonal antibodies and humanized antibodies, to treat include cancers of the breast, lung, small intestine (reads on gastrointestinal), colon, kidney, ovary, prostate, brain, pancreas, skin, bone, uterus, testicles, cervix and liver and in view of the fact that mab 1D11.16 inhibits binding of TGF-beta to its receptor and inhibits its function (as disclosed in Dasch et al) (in other words 1D11.16 is behaving as an antagonist), it

would have been obvious to one of ordinary skill in the art at the time of applicant's invention to use 1D11.16 to treat cancers of the breast, lung, small intestine (reads on gastrointestinal), colon, kidney, ovary, prostate, brain, pancreas, skin, bone, uterus, testicles, cervix and liver.

Claims 46-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dasch et al US 6090383 in view of WO 00/01410, Barbera-Guillem US 6224866, Rosenblum US 2005/0214307 (filed 3/17/95) and Zavada et al US 6297041 and Terabe et al Nature Immunology vol. 1 p. 515 (12/00).

Dasch et al, WO 00/01410, Barbera-Guillem, Rosenblum and Zavada et al have been discussed above. Dasch et al also disclose the use of the mab in an assay to monitor tumor mass (col. 6, lines 44-61). Thus, this reference is also disclosing methods for monitoring tumor progression (reads on tumor immunosurveillance).

The only difference between the instant invention and the reference is the specific mention of the specific assays used for tumor immunosurveillance.

Terabe et al shows that the assays of claims 56-58 are known in the art (see page 520, first column) and are used in tumor immunosurveillance (see entire reference).

Thus, in view of the known use of the assays for tumor immunosurveillance and in view of the fact that the primary reference calls for monitoring tumor progression, it

would have been obvious to one of ordinary skill in the art at the time of applicant's invention to use these assays to monitor tumor progression.

(10) Response to Argument

Response to arguments for the rejection of claims 46-50, 52-55, 59-67, 69 and 71 under 35 U.S.C. 103(a) as being unpatentable over Dasch et al US 6090383 in view of WO 00/01410, Barbera-Guillem US 6224866, Rosenblum US 2005/0214307 (filed 3/17/95) and Zavada et al US 6297041.

Appellant argues that the claims are directed to a method of inhibiting a tumor recurrence not to a method of treating and provides a declaration (June 5, 2009) to show that the actions of inhibiting and treating are very different and that treating cannot be equated to inhibiting. Appellant is under the impression that the Examiner is exclusively equating treating to inhibiting. This is not true. It is appellant's own specification that equates inhibiting to treating but as clearly discussed inhibiting is only a part of treating. On page 17, appellant defines treatment as including prophylactic inhibition (i.e. tumor recurrence (lines 11+). Furthermore, on page 2, lines 24-25 of the specification, appellant states "the disclosure provides methods of inhibiting tumor recurrence in a subject by administering a **therapeutically effective amount of an agent** to the subject" (emphasis added) and the definition of "therapeutically effective amount of an agent" gives an example of using the same anti-TGF-beta antibody to treat and inhibit tumor recurrence (see page 16, lines 32-33). Thus, appellant's own

specification equates treatment to inhibition. Furthermore, not only does appellant's specification equate inhibiting and treating, but the references also do this. The Zavada et al reference enables their treatment by showing examples of inhibition (see Examples 3-5) and in col. 8, lines 25+ shows that the treatment of patients with neoplastic diseases can be inhibited by administering the compounds of the invention. Dasch et al discloses that the therapeutically effective amount "inhibits" the tumor immunosuppressive growth which results in tumor regression. (col. 4, lines 15+). Rosenblum et al shows that the treatment of their compound is accomplished by inhibition of cell growth([0102]). Thus, the references and appellant's specification state that treatment reads on inhibition.

Appellant argues that the examiner has narrowly read the passage from page 16, lines 32-33 of the specification and that the intent of the passage was to be that the neutralizing antibody can be used to inhibit reoccurrence following any treatment of a tumor. The intent of the passage is true, but it seems appellant is implying that the antibody of the invention can only inhibit tumor recurrence after previous treatment and as shown by Dasch et al, which uses the same antibody as appellant, the same antibody can also be used in treatment.

Appellant argues that Dasch et al does not teach that the antibody can be used to treat tumor recurrence nor does Dasch et al disclose methods of inhibiting tumor recurrence. The Examiner has agreed to this. It is the combination of the primary reference and the secondary references which shows that it is known in the art that the same compound that is used to treat tumors and also treat/inhibit tumor recurrence.

Appellant cited the June 5, 2009 declaration as giving examples of compounds which are ineffective in treat the recurrence even though they can treat the tumor. The references cited to support this were not found and therefore the examiner cannot comment on these. However, in view of WO 00/01410, Rosenblum et al, Dasch et al and Zavada et al indicating that treatment reads on inhibition (that treatment can be enabled by showing inhibition), and in view of the fact that inhibition is a part of treatment, and since the references all indicate that compounds that treat tumors can be used in the treatment of tumor recurrence, the art still renders the claimed invention obvious.

Appellant argues that none of the secondary references teach anti-TGF-beta antibody or its ability to inhibit tumor recurrence. As stated in the rejection these references were cited to show what is known in the art-- it is known in the art that compounds that treat tumors can also be used to treat tumor recurrence.

Appellant states that antibodies are an unpredictable class of compounds and that the use of one antibody for one purpose (treatment) would not predict its use for an entirely different purpose (inhibition). As discussed above, inhibiting is a part of treating. Thus, the purposes are essentially the same. The secondary references were cited to show that it is well known in the art that antibodies in general are known to treat both tumors and tumor recurrence. Barbera-Guillem and Rosenblum disclose different antibodies with different actions and yet both antibodies are still able to treat both tumors and tumor recurrence. Thus, two different antibodies, which have different mechanisms of action can be used to treat both tumors and tumor recurrence. This is

further supported by Zavada which discloses a third antibody which has yet another mechanism of action and still can be used in the treatment of both tumors and tumor recurrence. In addition, the Examiner has added the reference WO 00/01410 and this adds further support to the Examiner's position because this reference clearly discloses antibodies to TGF-beta to be used to in the diagnosis and treatment of proliferating cells and that the diagnosis also includes diagnosing tumor recurrence. Thus, the prior art discloses the use of a generic class of compounds (i.e. different antibodies with different mechanisms of action) can achieve the same result.

Appellant argues that the combination of the reference does not predictably result in the claimed invention. Appellant and Examiner both agree that Dasch et al does not the treatment of tumor recurrence. Specifically, appellant argues that WO 00/01410 discloses the detection of quantification of TGF-beta as a measure of potential recurrence and not the use of antibody to inhibit tumor recurrence. The Examiner never stated that the reference discloses the inhibition of tumor recurrence. The reference discloses antibodies to TGF-beta and these are used in diagnosis and treatment of proliferating cells. Thus, this reference is saying that same compound can be used in the diagnosis and treatment. Furthermore, the reference states that the compounds can be used in the diagnosis of tumor recurrence. It logically follows that because compounds that can be used in the diagnosis and the treatment of tumors and can also be used in the diagnosis of tumor recurrence, one would immediately envisage that the compounds that can be used in the diagnosis of tumor recurrence can also be used in the treatment of tumor recurrence. The examiner is not equating detection with

inhibition, the examiner is saying that is known to be used in treatment and diagnosis of tumors and known to be used in the diagnosis of tumor recurrence, one skilled in the art would logically envisage the treatment of tumor recurrence. In response to this argument, appellant argues that antibodies are unpredictable and an agent used to measure a tumor/tumor recurrence does not necessarily mean that the same compound will treat/prevent/inhibit tumor recurrence--appellant cites PSA as an example of this. The Examiner has provided four (4) references each of which uses the same compound to treat/inhibit tumors and tumor recurrence. Appellant has only provided one such example. Appellant argues that Barbera-Guillem and Rosenblum disclose antibodies that have different activities, actions and results that the claimed 1D11.16 antibody. Appellant argues that Zavada et al use a different agent for treatment of tumors and treatment of tumor recurrence. As stated by appellant, Zavada et al states that anti-idiotypic antibodies are used to inhibit tumor recurrence (col. 10, line 50 to col. 11, line 10). In col. 49 (lines 20-30) the reference also discloses that anti-idiotypic antibodies have therapeutic anti-tumor efficacy. Thus, the reference does disclose using the same antibodies to treat tumors and inhibit tumor recurrence. With respect to Rosenblum, applicant argues that the reference cannot be predictive of the claimed methods because the reference uses a completely different antibody. This reference discloses that the same antibody used in treatment of tumors is used in the treatment of tumor recurrence. Since appellant's own specification equates treatment to inhibition/prevention the reference reads on appellant's own definitions. Appellant also argues that the antibody of the claimed invention blocks an immunosuppressive effect

of TGF-beta versus the direct targeting of the antibody of Rosenblum. The antibody of the primary reference (which is the same antibody used by applicant in the claimed invention) does suppress the immunosuppressive effects of TGF-beta and thus since the secondary references show that the same antibody or antibody can be used to both treat and inhibit/prevent tumors and tumor recurrence, the antibody of the primary reference can also be used to both treat and inhibit/prevent tumors and tumor recurrence.

Appellant argues that the combination of the references does not teach the method of claim 60 or claim 63--specifically a "method of enhancing an activity of an immune cell to inhibit recurrence of a tumor" or ""method of enhancing an immune response in a subject to inhibit recurrence. As stated in the rejection Mab 1D11.16 "neutralizes the biological activity of TGF-beta and prevents binding of antigen to cell surface receptors". "The biological activities of TGF-beta include suppressing the proliferation of T and B cells and NK cells and that the Mab of the invention blocks the TGF-B's immunosuppressive effects." Thus, since the antibody neutralizes that biological activity of TGF-beta and a biological activity of TGF-beta is suppressing proliferation of T and B cells (i.e. immune cells), the antibody of the reference suppress proliferation of immune cells--and this translates to an enhanced activity of the immune cell which results in an enhanced immune response.

Response to arguments against the rejection of claims 46-55, 59-72 under 35 U.S.C. 103(a) as being unpatentable over Dasch et al US 6090383 in view of WO

00/01410, Barbera-Guillem US 6224866, Rosenblum US 2005/0214307 (filed 3/17/95) and Zavada et al US 6297041 and Suthanthiran et al US 2004-0197333 (filed 2/10/00).

Appellant argues that the Suthanthiran et al reference does not teach all the elements of the claimed invention. The Examiner agrees to this because as stated in the rejection this reference was cited to show that it is known in the art the TGF-beta antagonists (including monoclonal antibodies) are known to treat a variety of different cancers and that the monoclonal antibodies can be humanized.

Appellant again argues that inhibiting does not equate to treating. This has been addressed above.

Appellant again argues that the WO 00/01410, Barbera-Guillem, Rosenblum and Zavada et al reference are not predictable. This argument has been addressed above.

Appellant again argues that the references do not meet the limitations of claims 60 and 63. This has been addressed above.

Response to arguments against the rejection of claims 46-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dasch et al US 6090383 in view of WO 00/01410, Barbera-Guillem US 6224866, Rosenblum US 2005/0214307 (filed 3/17/95) and Zavada et al US 6297041 and Terabe et al Nature Immunology vol. 1 p. 515 (12/00).

Appellant argues that the Terabe et al reference does not teach all the elements of the claimed invention. The Examiner agrees to this because as stated in the

rejection this reference was cited to show that the assays used in claims 56-58 are known in the art to be used to tumor immunosurveillance.

Appellant again argues that the WO 00/01410, Barbera-Guillem, Rosenblum and Zavada et al reference are not predictable. This argument has been addressed above.

Appellant again argues that the references do not meet the limitations of claims 60 and 63. This has been addressed above.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Sheela J. Huff/

Primary Examiner, AU 1643

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